1 PRODUCT NAME

Ketorolac Kabi 30 mg/1 mL solution for intramuscular injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketorolac trometamol 30 mg/mL
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for intramuscular injection

Ketorolac Kabi is available as a 30 mg/mL (3%) sterile solution for injection for intramuscular (IM) administration only. The injection solution is clear and slightly yellow in colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketorolac Kabi is indicated for the short-term management of moderately severe, acute pain following surgical procedures. The total duration of ketorolac use should not exceed five days.

It is recommended that ketorolac parenteral be used in the immediate post-operative period. Patients can then be converted to the oral* formulation (dependent on their analgesic needs), as outlined in section 4.2 **Dose and method of administration** ***(Conversion from intramuscular to oral therapy). The total period of treatment utilising the oral and/or intramuscular route of administration is not to exceed five days.***

** ketorolac oral formulation is available from other brands.*

General

Ketorolac is not recommended for use as an obstetrical pre-operative medication or for obstetrical analgesia because it has not been adequately studied for use in these circumstances and because the known effects of drugs that inhibit prostaglandin biosynthesis on uterine contraction and foetal circulation.

There is no satisfactory evidence for the use of ketorolac in acute exacerbations of chronic painful inflammatory conditions (e.g. rheumatoid or osteoarthritis).

4.2 Dose and method of administration

WARNING

Ketorolac is a potent NSAID analgesic and the resulting NSAID-related adverse effects can be serious, for example gastrointestinal haemorrhage, surgical haemorrhage and renal impairment.

Increasing the dose of ketorolac beyond the recommendations in the data sheet will not provide better efficacy but will result in increasing risk of developing serious adverse effects.

Ketorolac dosage should be adjusted according to the severity of the pain and the response of the patient. **The lowest effective dose should be used for the shortest possible time in all patient populations.**

Opiate analgesics (e.g. morphine and pethidine) may be used concomitantly, and may be required for optimal analgesic effect in the early post-operative period when pain is most severe, or when the anxiolytic effects and/or sedative effects of opiates are desired. Ketorolac has been administered with morphine in several clinical trials of post-operative pain without evidence of adverse interactions. Ketorolac does not exacerbate opioid-related respiratory depression or sedation. When used in association with intramuscular ketorolac, the daily dose of opioid is usually less than that which is normally required.

Hypovolaemia should be corrected prior to administration of ketorolac.

The total duration of ketorolac administration should not exceed 5 days because adverse effects may increase with prolonged usage.

Intramuscular administration

The intramuscular injection should be given slowly and deeply into the muscle.

Adults (under 65 years of age)

The usual recommended initial intramuscular dose is 10 mg to 30 mg, followed by 10 mg to 30 mg at 4 to 6 hourly intervals, up to a maximum daily dose of 90 mg.

Elderly (65 years of age and older)

An initial intramuscular dose of 10 mg to 15 mg, followed by 10 mg to 15 mg at 4 to 6 hourly intervals, up to a maximum daily dose of 60 mg.

Mild renal impairment

If ketorolac is used in patients with mildly impaired renal function (serum creatinine values: males between 130 and 180 micromol/L; females between 120 and 180 micromol/L) the lower end of the intramuscular dosage range should be used. The total daily dose should not exceed 60 mg. Ketorolac is contraindicated in patients with more severe degrees of renal impairment (refer section 4.3 **Contraindications**).

Cardiovascular

Patients on long-term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Other

For patients under 50 kg in body weight or for patients with less severe pain, the lower end of the intramuscular ketorolac dosage range is recommended. The total daily dose should not exceed 60 mg.

Ketorolac Kabi solution for injection is intended for use in one patient on one occasion only. Discard any residue.

Conversion from intramuscular to oral therapy

For patients being converted from intramuscular ketorolac to oral ketorolac, the total combined daily dose should not exceed 90 mg (60 mg for the elderly, mild renally-impaired patients and patients weighing less than 50 kg) and the oral component should not exceed

40 mg (30 mg to 40 mg for the elderly) on the day the change of formulation is made. Patients should be converted to oral treatment as soon as possible.

This brand does not include an oral presentation; therefore patients who need to be converted to oral therapy should be converted onto another brand.

4.3 Contraindications

Ketorolac is contraindicated in patients:

- with severe heart failure (refer section 4.4 **Special warnings and precautions for use** – Heart failure)
- undergoing treatment of perioperative pain in setting of coronary artery surgery
- with dehydration or hypovolaemia from any other cause
- with severe hepatic impairment
- with moderate or severe renal impairment (serum creatinine > 180 micromol/L) or in patients at risk of renal failure due to volume depletion or dehydration (refer section 4.4 **Special warnings and precautions for use** – Renal effects)
- with active, or a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) (refer section 4.4 **Special warnings and precautions for use** – Gastrointestinal effects)
- with a history of haemorrhagic diatheses, including coagulation disorders (refer section 4.4 **Special warnings and precautions for use** – Haematologic effects)
- who have had surgery with a high risk of haemorrhage or incomplete haemostasis; and those at high risk of bleeding (refer section 4.4 **Special warnings and precautions for use** – Haematologic effects)
- with suspected or confirmed cerebrovascular (intracranial) bleeding (refer section 4.4 **Special warnings and precautions for use** – Haematologic effects)
- on anticoagulation therapy (refer section 4.5 **Interaction with other medicines and other forms of interaction**)
- receiving aspirin, other NSAIDs, oxpentifylline, probenecid or lithium (refer section 4.5 **Interaction with other medicines and other forms of interaction**)
- with hypersensitivity to Ketorolac trometamol or other NSAIDs and those patients in whom aspirin or other prostaglandin synthetase inhibitors induce allergic reactions. Severe anaphylactic-like reactions have been observed in such patients. If such symptoms occur during therapy, treatment should be discontinued (refer section 4.4 **Special warnings and precautions for use** – Anaphylactic reactions)
- with the complete or partial syndrome of nasal polyps, angioedema or (refer section 4.4 **Special warnings and precautions for use** – Anaphylactic reactions)
- with a history of asthma (refer section 4.4 **Special warnings and precautions for use** – Anaphylactic reactions)
- with a prior history of Stevens-Johnson syndrome or vesicular bullous rash (refer section 4.4 **Special warnings and precautions for use** – Severe skin effects and section 4.8 **Undesirable effects**)

Ketorolac Kabi is contraindicated for:

- neuraxial (epidural or intrathecal) administration due to its ethanol content
- prophylactic administration before surgery, due to inhibition of platelet aggregation, and intraoperatively because of the increased risk of bleeding

- use in pregnancy, labour, delivery or lactation (refer section 4.6 **Fertility, pregnancy and lactation**)
- children under 16 years of age.

4.4 Special warnings and precautions for use

Cardiovascular thrombotic events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (refer section 4.2 **Dose and method of administration**). Although ketorolac has not shown to increase thrombotic events such as myocardial infarction, there are insufficient data to exclude such a risk for ketorolac.

Physicians and patients should remain alert for such CV events even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention, cardiac decompensation, heart failure, hypertension or similar conditions.

Gastrointestinal effects

Ketorolac can cause gastrointestinal irritation, ulcers, perforation or bleeding, which can be fatal, at any time, with or without warning symptoms or a previous history of serious gastrointestinal events.

Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months and in about 2–4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal effect at some time during the course of therapy. However, even short-term therapy is not without risk.

The risk of gastrointestinal bleeding, ulceration or perforation increases with dose and duration of treatment; in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation; in the elderly; and in those with a history of smoking or alcoholism. Caution is advised in these patients and treatment should commence on the

lowest dose available. Combination therapy with gastro-protective agents (e.g. misoprostol or proton-pump inhibitors) should be considered for these patients.

Elderly and debilitated individuals are more susceptible to gastrointestinal complications (refer section 4.2 **Dose and method of administration** – *Elderly*, for dosage reductions in this patient group). Most reports of fatal gastrointestinal effects are in this population.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis; Crohn's disease) as their condition may be exacerbated.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrointestinal ulceration or bleeding, such as NSAIDs, oral corticosteroids; anticoagulants such as warfarin; selective serotonin reuptake inhibitors (SSRIs); or anti-platelet agents such as aspirin, as these combinations may increase the risk of serious gastrointestinal adverse effects (refer section 4.5 **Interaction with other medicines and other forms of interaction**). Combination therapy with gastro-protective agents (e.g. misoprostol or proton-pump inhibitors) should be considered for these patients.

Prescribers should warn patients about the signs and symptoms of serious gastrointestinal toxicity. Patients administered Ketorolac Kabi should be instructed to advise their physician immediately if they experience any unusual abdominal symptoms (especially gastrointestinal bleeding). Ketorolac Kabi should be discontinued, appropriate treatment instituted and the patient closely monitored.

In a non-randomised, in-hospital post-marketing surveillance study, increased rates of clinically serious gastrointestinal bleeding were seen in patients 65 years of age and under who received an average daily dose of greater than 90 mg ketorolac administered intramuscularly as compared to those patients receiving parenteral opioids.

Renal Effects

As with other NSAIDs that inhibit prostaglandin biosynthesis, elevations of serum urea, nitrogen, potassium and creatinine have been reported in clinical trials with ketorolac, and can occur after one dose. Ketorolac trometamol and its metabolites are eliminated primarily by the kidneys which, in patients with reduced creatinine clearance, will result in diminished clearance of the medicine. **Patients with moderate to severe impairment of renal function should not receive ketorolac** (refer section 4.2 **Dose and method of administration** – *Mild Renal Impairment*, for dosage reduction in patients with mild renal impairment i.e. serum creatinine < 180 micromol/L). Ketorolac should be used with caution in patients with a history of kidney disease. Renal function should be monitored in patients who have had more than a single intramuscular dose of ketorolac, particularly in elderly patients.

As with other NSAIDs that inhibit prostaglandin biosynthesis, the following renal abnormalities may be associated with the use of ketorolac: glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, acute renal failure and hyperkalaemia. Other renal conditions/diseases are possible.

Caution should be observed in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal failure. Patients at greatest risk of this effect are those who are volume depleted because of blood loss or severe dehydration, patients with impaired renal function, heart failure, liver

dysfunction, the elderly and those taking diuretics. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state Inadequate fluid/blood replacement during surgery, leading to hypovolaemia (refer section 4.3 **Contraindications**), may lead to renal dysfunction which could be exacerbated when ketorolac is administered. Therefore, volume depletion should be corrected and close monitoring of serum urea, serum creatinine and urine output is recommended until the patient is normovolaemic. In patients on renal dialysis, ketorolac clearance is reduced to approximately half the normal rate and terminal half-life increases approximately three-fold.

Haematologic effects

Ketorolac inhibits platelet aggregation and may prolong bleeding time. Unlike the prolonged effects from aspirin, the inhibition of platelet function by ketorolac resolves within 24–48 hours after the medicine is discontinued. Ketorolac does not affect platelet count, prothrombin time or partial thromboplastin time. In controlled clinical studies, the incidence of clinically significant post-operative bleeding was 5/1170 (0.4%) compared to 1/570 (0.2%) in the control groups receiving opiates.

The use of ketorolac in patients who have coagulation disorders should be undertaken very cautiously, and those patients carefully monitored. PATIENTS ON ANTICOAGULATION THERAPY (e.g. HEPARIN OR WARFARIN) MAY BE AT INCREASED RISK OF BLEEDING IF GIVEN KETOROLAC CONCURRENTLY (refer to CONTRAINDICATIONS). The concomitant use of ketorolac and prophylactic low-dose heparin has not been studied extensively and may also be associated with an increased risk of bleeding. Concomitant administration of dextrans may also increase the risk of post-operative bleeding. Patients receiving other medicines that affect haemostasis should be carefully observed if ketorolac is administered (refer section 4.5 **Interaction with other medicines and other forms of interaction**).

In post-marketing experience, post-operative wound haemorrhage has been reported in association with the immediate peri-operative use of intramuscular ketorolac. Therefore, ketorolac should not be used in patients who have had surgery with a high risk of haemorrhage or incomplete haemostasis. Caution should be used where strict haemostasis is critical, e.g. in cosmetic or day care surgery, resection of the prostate or tonsillectomy. Haematomata, other signs of wound haemorrhage and epistaxis have been reported with the use of ketorolac. Physicians should be aware of the pharmacological similarity of ketorolac to other NSAIDs that inhibit cyclo-oxygenase and the risk of bleeding, particularly in the elderly.

Hepatic effects

As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) have been reported in controlled clinical trials (with the oral formulation of ketorolac trometamol) in less than 1% of patients. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash etc.), ketorolac should be discontinued.

Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac clearance. Studies to assess the pharmacokinetics of ketorolac in patients with active hepatitis or cholestasis have not been done. Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity.

A patient with symptoms and/or signs suggesting liver dysfunction (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms), or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic effects while on therapy with Ketorolac.

Severe skin effects

NSAIDs may very rarely cause serious cutaneous adverse effects such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal and occur without warning. These serious adverse effects are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin effects and to consult their physician at the first appearance of a skin rash or other sign of hypersensitivity.

Injection site effects

Ketorolac injection administered intramuscularly has produced pain at the injection site in 2 to 4% of patients. Ecchymosis, bruising, haematoma and tingling at the injection site have rarely been reported. Adverse local effects may be minimised by applying pressure at the injection site for 15 to 30 seconds after administration. There has been no evidence (e.g. alterations in serum creatine kinase [CK] or creatine phosphokinase [CPK] concentrations) of substantial adverse muscular tissue effects following single or multiple intramuscular injections of ketorolac.

Anaphylactic reactions

Anaphylactic (anaphylactoid) reactions (including, but not limited to, anaphylaxis, bronchospasm, flushing, rash, hypotension, laryngeal oedema and angioedema) may occur in individuals with or without a history of hypersensitivity to aspirin, other NSAIDs, or ketorolac. These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma) and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Therefore, ketorolac should be used with caution in patients with a history of asthma and in patients with the complete or partial syndrome of nasal polyps, angioedema and bronchospasm.

Special senses

Adverse ophthalmological effects have been observed with non-steroidal anti-inflammatory agents; accordingly, patients who develop visual disturbances during treatment with ketorolac should have an ophthalmological examination.

Drug abuse and physical dependence

Ketorolac is not a narcotic agonist or antagonist. Subjects did not show any subjective symptoms or objective signs of drug withdrawal upon abrupt discontinuation of intramuscular dosing. Ketorolac did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action (hot plate and tail withdrawal test). *In vitro* ketorolac does not bind to opiate receptors. These studies demonstrate that ketorolac does not have central opiate-like activity.

General

Undesirable effects may be minimised by using the lowest minimum effective dose for the shortest duration necessary to control symptoms (refer section 4.2 **Dose and method of administration**).

Ketorolac is not an anaesthetic agent and possesses no sedative or anxiolytic properties, therefore it is not recommended as a pre-operative or intra-operative medication for the support of anaesthesia when these effects are required. Ketorolac Kabi should not be used for spinal or epidural administration, as it Kabi contains ethanol 10% (refer section 4.3 **Contraindications**).

The total duration of ketorolac treatment should not exceed five days.

Paediatric population

The safety and efficacy in children have not been established, therefore, ketorolac is not recommended for use in children under 16 years of age (refer to CONTRAINDICATIONS).

Use in the elderly

Because ketorolac trometamol is cleared somewhat more slowly by the elderly (refer section 5.2 **Pharmacokinetic properties**) who are also more sensitive to the fluid retaining, gastrointestinal toxicity and renal impairment effects of ketorolac, extra caution and the lowest effective dose should be used when treating the elderly with ketorolac (refer section 4.2 **Dose and method of administration**).

4.5 Interaction with other medicines and other forms of interaction

Protein binding

Ketorolac is highly bound to human plasma protein (mean 99.2%) and binding is independent of concentration. The *in vitro* binding of warfarin to plasma proteins is only slightly reduced by ketorolac (99.5% control vs. 99.3% binding with ketorolac concentrations of 5–10 µg/mL). Ketorolac does not alter digoxin protein binding.

In vitro studies indicated that at therapeutic concentrations of salicylate (300 µg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, paracetamol, phenytoin, tolbutamide and piroxicam did not alter ketorolac protein binding. Because ketorolac is a highly potent medicine and present in low concentrations in plasma, it would not be expected to displace other protein bound medicines significantly.

Enzyme induction/inhibition

There is no evidence in animal or human studies that ketorolac induces or inhibits the hepatic enzymes capable of metabolising itself or other medicines. Hence, ketorolac would not be expected to alter the pharmacokinetics of other medicines due to enzyme induction or inhibition mechanisms.

Warfarin

The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage. The exact mechanism of the interaction between NSAIDs and warfarin is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Ketorolac should be used in combination with warfarin only if absolutely necessary, and patients taking this combination of medicines should be closely monitored.

Anticoagulant therapy and other drugs affecting haemostasis

NSAIDs may enhance the effects of anti-coagulants, such as warfarin, low-molecular weight heparin and dextrans (refer section 4.3 **Contraindications** and section 4.4 **Special warnings**

and precautions for use – Haematologic effects). Unlike the prolonged effects from aspirin, platelet function returns to normal within 24–48 hours after ketorolac is discontinued.

Aspirin and other NSAIDs

In patients concurrently receiving aspirin or other NSAIDs, the risk of inducing serious NSAID-related adverse effects may be increased (refer section 4.3 **Contraindications**).

Oxpentifylline

When ketorolac is administered concurrently with oxpentifylline, there is an increased tendency to bleeding (refer section 4.3 **Contraindications**).

Probenecid

Concomitant administration of oral ketorolac and probenecid resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 µg/h/mL) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore the concomitant use of ketorolac and probenecid is contraindicated.

Lithium

Inhibition of renal lithium clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis-inhibiting medicines. The effect of ketorolac on plasma lithium has not been studied, but cases of increased plasma levels during ketorolac therapy have been reported.

Methotrexate

Concomitant administration of methotrexate and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of ketorolac on methotrexate clearance has not been studied.

ACE-Inhibitors

As with other NSAIDs, ketorolac may increase the risk of renal impairment associated with the use of ACE-inhibitors, particularly in patients that are actually or effectively volume depleted.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory medicines and thiazide diuretics (Triple Whammy)

The use of an ACE inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory medicine (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time (Triple Whammy) increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of medicine. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly during initiation of the combination. The combination of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Diuretics

Ketorolac reduces the diuretic response to frusemide in normovolaemic healthy subjects by approximately 20%.

Nephrotoxic agents

The use of medicines with nephrotoxic activity (e.g. aminoglycoside antibiotics) should be avoided when using ketorolac.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when anti-platelet agents and SSRIs are combined with NSAIDs.

Antiepileptic medicines

Sporadic cases of seizures have been reported during concomitant use of ketorolac and antiepileptic medicines (phenytoin, carbamazepine).

Psychoactive medicines

Hallucinations have been reported when ketorolac was used in patients taking psychoactive medicines (fluoxetine, thiothixene, alprazolam).

4.6 Fertility, pregnancy and lactation

Pregnancy

Ketorolac is not recommended for use during pregnancy, labour and delivery (refer section 4.3 **Contraindications**).

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Breast-feeding

Ketorolac is not recommended for treatment of nursing mothers (refer section 4.3 **Contraindications**).

After a single oral administration of 10 mg ketorolac to humans, the maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025.

Fertility

Ketorolac may impair fertility and is not recommended in women attempting to conceive.

4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of ketorolac. If patients experience these, or other similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 Undesirable effects

Parenteral administration

Physicians using ketorolac Injection should be alert for the usual complications of non-steroidal anti-inflammatory treatment.

The adverse effects listed below were reported to be probably related to ketorolac in clinical trials in which patients received up to 20 doses, in five days, of **post-operatively** administered

ketorolac 30 mg intramuscularly and in clinical trials in which patients received up to 8 doses in two days, of **post-operatively** administered ketorolac 30 mg intravenously.

Incidence between 3% and 9%

- Gastrointestinal disorders: nausea, dyspepsia, gastrointestinal pain.
- Nervous system disorders: drowsiness.

Incidence between 1% and 3%

- Gastrointestinal disorders: diarrhoea.
- General disorders and Administration site conditions: oedema, injection site pain was reported by 2% of patients in multi-dose studies (compared with 5% for the morphine control group).
- Nervous system disorders: dizziness, headache.
- Skin and subcutaneous tissue disorders: sweating.

Incidence 1% or less

- Ear disorders: vertigo.
- Eye disorders: abnormal vision.
- Gastrointestinal disorders: constipation, flatulence, gastrointestinal fullness, liver function
- abnormalities, melaena, peptic ulcer, rectal bleeding, stomatitis, vomiting.
- General disorders and administration site conditions: asthenia, excessive thirst.
- Musculoskeletal and connective tissue disorders: myalgia.
- Nervous system disorders: dry mouth, paraesthesia, stimulation, abnormal taste.
- Psychiatric disorders: nervousness, abnormal thinking, depression, euphoria, insomnia, inability to concentrate.
- Renal and urinary disorders: increased urinary frequency, oliguria.
- Respiratory, thoracic and mediastinal disorders: dyspnoea,asthma
- Skin and subcutaneous tissue disorders: pruritus, urticaria, purpura.
- Vascular disorders: vasodilation, pallor.

<u>Oral administration</u>

(ketorolac oral formulation is available from other brands)

The incidence of adverse effects in approximately 600 patients and subjects receiving **short-term** oral therapy with the 10 mg tablet (**less than 2 weeks**) are listed below.

Incidence between 1% and 2%

- Gastrointestinal disorders: nausea, dyspepsia, gastrointestinal pain.
- Nervous System disorders: dizziness,headache.
- Vascular disorders: hypertension.

Incidence 1% or less

- Gastrointestinal disorders: flatulence, gastritis.
- General disorders and administration site conditions: asthenia, oedema.
- Musculoskeletal and connective tissue disorders: myalgia.
- Respiratory, thoracic and mediastinal disorders: dyspnoea.
- Skin and subcutaneous tissue disorders: urticaria, rash, pruritus, purpura.

<u>Post-marketing adverse effects</u>

The following international post-marketing adverse effects, although rare, have been reported spontaneously for patients who have received ketorolac trometamol.

- Blood and lymphatic system disorders: thrombocytopenia, epistaxis, haematoma, angioedema.
- Cardiac disorders: bradycardia, palpitations, cardiac failure.
- Ear disorders: hearing loss, tinnitus, vertigo.
- Eye disorders: abnormal vision.
- Gastrointestinal disorders: gastrointestinal haemorrhage, peptic ulceration, gastrointestinal perforation, nausea, vomiting, diarrhoea, flatulence, eructation, constipation, dyspepsia, abdominal pain/discomfort, melaena, haematemesis, stomatitis, ulcerative stomatitis, oesophagitis, rectal bleeding, pancreatitis, dry mouth, fullness, exacerbation of colitis and Crohn's disease, gastritis.
- General disorders and administration site conditions: weight gain, injection site reactions, pallor, fever, asthenia, oedema, excessive thirst, chest pain.
- Hepatobiliary disorders: hepatitis, cholestatic jaundice, liver failure.
- Immune system disorders: anaphylaxis, anaphylactoid reactions, hypersensitivity reactions such as flushing, rash, hypotension, bronchospasm and laryngeal oedema (refer section 4.4 **Special warnings and precautions for use** – Anaphylactic Reactions).
- Infection: infection, aseptic meningitis
- Investigations: abnormal liver function tests, increased serum urea, increased creatinine, prolonged bleeding time.
- Metabolic and nutrition disorders: hyponatraemia, hyperkalaemia, anorexia.
- Musculoskeletal and Connective Tissue disorders: myalgia.
- Nervous system disorders: headache, dizziness, paraesthesia, convulsions, extrapyramidal symptoms, hyperkinesia, taste abnormality, dry mouth, drowsiness.
- Psychiatric disorders: abnormal dreams, hallucinations, anxiety, psychotic reactions, abnormal thinking, depression, insomnia, nervousness, euphoria, impaired concentration ability.
- Renal and Urinary disorders: acute renal failure, urinary retention, increased urinary frequency, interstitial nephritis, nephrotic syndrome, haemolytic uraemic syndrome, oliguria, flank pain with or without haematuria and/or azotemia (refer section 4.4 **Special warnings and precautions for use** – Renal Effects).
- Reproductive system and breast disorders: female infertility.
- Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, pulmonary oedema.
- Skin and subcutaneous tissue disorders: rash, Stevens-Johnson syndrome (SJS), exfoliative dermatitis, toxic epidermal necrolysis (TEN), maculopapular rash, Lyell's syndrome, pruritus, urticaria, purpura, sweating.
- Vascular disorders: hypotension, hypertension, flushing, pallor, post-operative wound
- haemorrhage (rarely requiring blood transfusion).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and signs

Single overdoses of ketorolac have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment

Patients should be managed by symptomatic and supportive care following NSAID overdose. There are no specific antidotes. Dialysis does not significantly clear ketorolac from the blood stream.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	Anti-inflammatory and antirheumatic products, non-steroids Acetic acid derivatives and related substances
ATC code:	M01AB15

Mechanism of action

Ketorolac is a non-narcotic analgesic belonging to the non-steroidal anti-inflammatory drug (NSAID) class of medicines with analgesic, anti-inflammatory and antipyretic properties.

Ketorolac trometamol inhibits the cyclo-oxygenase enzyme system and hence synthesis of prostaglandins. It is considered to be a peripherally-acting analgesic. It does not have known effects on opiate receptors. It has no intrinsic effects on respiration and does not exacerbate opioid-related respiratory depression or sedation. Ketorolac trometamol has no significant CNS effects in animals and possesses no sedative or anxiolytic properties.

Clinical efficacy and safety

Intramuscular

Controlled clinical trials studying acute severe pain following major surgical procedures such as cholecystectomy, gastric bypass, abdominal hysterectomy, open reduction and fixation of fractures, lumbar laminectomy, and extraction of multiple impacted third molar teeth, have established the efficacy of ketorolac relative to other analgesics.

Given post-operatively, ketorolac 30 mg IM has an onset of action and peak analgesic efficacy comparable to morphine 12 mg IM or pethidine 100 mg IM, and is more effective than morphine 6 mg IM or pethidine 50 mg IM.

Ketorolac 30 mg IM has a longer duration of action than morphine 12 mg IM or pethidine 100 mg IM. Ketorolac 10 mg IM gives efficacy equal to or greater than morphine 6 mg IM or pethidine 50 mg IM.

*Oral**

(* ketorolac oral formulation is available from other brands)

Comparative controlled clinical trials studying acute pain following extraction of impacted third molars and orthopaedic, abdominal and gynaecological surgery have established the analgesic efficacy of oral ketorolac trometamol. In a series of clinical trials, ketorolac tablets 10 mg have been found superior or equal to aspirin 650 mg, paracetamol 600 mg and 1000 mg,

paracetamol 600 mg plus codeine 60 mg, paracetamol 1000 mg plus codeine 60 mg, and ibuprofen 400 mg.

5.2 Pharmacokinetic properties

The pharmacokinetics of ketorolac in young healthy adult volunteers following single or multiple IM or recommended oral doses are linear.

Absorption

The IM form of ketorolac is rapidly and completely absorbed (100% bioavailable). Steady state plasma levels are achieved after dosing every 6 hours for one day. A mean peak plasma concentration of 2.2 µg/mL occurs an average of 50 minutes after a single 30 mg dose.

Orally administered ketorolac is rapidly and completely absorbed with a peak plasma concentration of 0.52 to 1.31 µg/mL occurring 35 minutes after a single 10 mg dose in fasted subjects. A high fat diet decreased the rate, but not the extent of absorption, while antacid had no effect upon ketorolac absorption.

Binding and Distribution

More than 99% of ketorolac in plasma is protein bound. Even at high plasma concentrations (10 µg/mL) only approximately 5% of albumin binding sites will be occupied. Thus the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

Plasma protein binding is independent of concentration. As ketorolac trometamol is a highly potent medicine and present in low concentrations in plasma, it would not be expected to displace other protein-bound medicines significantly.

Nearly all the medicine-related material circulating in plasma is ketorolac (96%) or the pharmacologically inactive p-hydroxyketorolac.

The mean apparent volume (V_β) of ketorolac trometamol following complete distribution is approximately 13 litres (this parameter was determined from single dose data).

Ketorolac trometamol poorly penetrates the blood brain barrier (levels in the cerebrospinal fluid were found to be 0.002 times or less than those in plasma).

Ketorolac crosses the placenta (mean umbilical/maternal vein concentration ratio for ketorolac was 0.116 and this ratio increased as the time from injection to sampling increased). Ketorolac has been detected in human milk at low concentrations (refer to section 4.6 **Fertility, pregnancy and lactation**).

Metabolism

Ketorolac trometamol is largely metabolised in the liver. The major metabolic path of ketorolac in humans is glucuronic acid conjugation. P-hydroxylation is an additional minor pathway.

Excretion

The primary route of excretion of ketorolac and its metabolites (conjugates and a para-hydroxy metabolite) is in the urine (mean 91.4%) and the remainder (mean 6.1%) is excreted in the faeces. The terminal plasma half-life of ketorolac is approximately in the range of 5–6 hours. No changes in clearance occur with chronic dosing.

Pharmacokinetics in special populations

Elderly patients (65 years of age or older)

In the elderly, the mean terminal plasma half-life of ketorolac increases from 5 to 7 hours compared with young healthy volunteers (based on single dose data) (refer to section 4.2 **Dose and method of administration**). There is little difference in the C_{max} for the two groups.

Renally-impaired patients

The mean half-life of ketorolac in renally-impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment (based on single dose data). There is poor correlation between creatinine clearance and total ketorolac trometamol clearance in the elderly and populations with renal impairment (r = 0.5). In patients with renal disease, the AUC increases by approximately 100% compared with healthy volunteers. The volume of distribution increases by up to 100%. The increase in volume of distribution of ketorolac trometamol implies an increase in unbound fraction. The AUC ratio of the ketorolac trometamol enantiomers in healthy subjects and patients remains similar, indicating there is no selective excretion of either enantiomer in patients compared to healthy subjects.

Hepatically-impaired patients

Patients with impaired hepatic function do not have any clinically important changes in ketorolac pharmacokinetics, although there is a statistically significant prolongation of T_{max} and terminal phase half-life compared to young healthy volunteers.

5.3 Preclinical safety data

Reproduction studies with ketorolac have been performed in rabbits and rats at oral doses of 3.6 and 10 mg/kg/day, respectively. The results from these studies did not reveal any significant evidence of harm to the fetus. However, studies in rabbits have shown a small increase in the incidence of major vessel anomalies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Sodium chloride
Water for injections
Sodium hydroxide or hydrochloric acid (pH adjustment).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

1 mL solution in amber-coloured, tubular glass vials.
Available in packs of 5s.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Airport Oaks, Auckland 2022
New Zealand

Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
13 April 2018.

10 DATE OF REVISION OF THE TEXT

20th April 2018.

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
n.a.	New data sheet